2015

National Heart, Lung, and Blood Institute

# Draft Strategic Research Priorities

## Message from Dr. Gary Gibbons
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Thank you to all who contributed to NHLBI's Strategic Visioning process. Ultimately, over 1,000 ideas were submitted to the Strategic Visioning Forum with more than 42,000 votes. This remarkable response exceeded expectations and provided a wealth of ideas to draw upon as NHLBI moves forward.

NHLBI staff and advisory groups evaluated the ideas submitted to the Forum, leading to the preliminary set of high-priority Compelling Questions and Critical Challenges below. We have posted this refined set of Compelling Questions and Critical Challenges as part of our efforts to keep the community informed and engaged.

In September, the NHLBI advisory groups will convene again to further refine the Compelling Questions and Critical Challenges. We plan to release a final list of Strategic Research Priorities for public comment in the fall. The final Strategic Vision will be released in early 2016.

# Goal 1: Promote Human Health

| ID No. | CQ/CC |
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| **Theme A. Information Management and Modeling** | |
| **Theme A Rationale:** *Large amounts of information have been generated as a result of the "omics" revolution and the ability to access phenotypic information electronically. Computational biology modeling approaches need to be developed to compile and integrate these data in robust datasets using common languages to allow for their optimal evaluation. The analysis of such large, complex and integrated data sets will stimulate development of predictive models of how heart, lung, blood, and sleep (HLBS) systems react in different environments and will help identify protective or at-risk phenotypes.* | |
| **1.A.1** | CC: There is a need to create tools to access and analyze electronic medical records (EMR) data and its linkage to "-omics." The critical challenge is how to facilitate multi-stakeholder interactions to create a common language, aggregate dataset, and analysis pipeline for EMR data which can be linked with other datasets, including phenomics, genomics, and metabolomics. |
| **1.A.2** | CC: There is a need to catalyze the development, application, and sharing of robust and multidimensional data-analytical and theoretical methods, mathematical modeling, and computational simulation techniques in order to fully understand normal variations in HLBS systems and their relationships. |
| **Theme B. Mechanistic Interactions Between HLBS Systems and Other Body Systems: a Holistic Approach** | |
| **Theme B Rationale:** *The interplay between our body systems and our close relationship with the many bacteria, viruses and other microorganisms that inhabit us – or microbiome – define in part how our body functions. The interactions among HLBS systems and the effect of our body clocks, microbiome, nervous, lymphatic, and immune systems on HLBS homeostasis need to be understood. For example, defining the interplay between the immune, the lymphatic, and the HLBS systems is necessary to our understanding of how normal and dysregulated function in one system may impact the structure and function of another system.* | |
| **1.B.1** | CQ: What are the molecular and cellular physiologic characteristics of the innate and adaptive immune systems that promote HLBS health and prevent phenotypic expression of HLBS diseases? |
| **1.B.2** | CQ: How can we "reprogram" the immune system to improve outcomes of allogeneic cell therapies, tissue and organ transplants, and regenerative strategies, and to diminish allogeneic responses to essential biologic replacement therapies? |
| **1.B.3** | CQ: What brain areas and mechanisms mediate the interactions between the brain and cardiovascular systems involved with physiological and psychological stress? |
| **1.B.4** | CQ: What is the role of the lymphatic system in sustaining HLBS health? |
| **1.B.5** | CQ: What is the influence of the microbiome, such as that in the lung, gut, and oral cavity, on the immune system and HLBS health, including development processes across the normal human lifespan? |
| **1.B.6** | CQ: What are the unknown elements of the human virome, and how do interactions of the virome with the host and the rest of the microbiome affect HLBS health and disease risk? |

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| **1.B.7** | CQ: Does circadian regulation modify the effects of environmental exposures (e.g., cigarette smoke, particulates, viruses or bacteria, temperature, humidity) on mechanisms of HLBS function? |
| **1.B.8** | CQ: What are the basic mechanistic pathways underlying the effects of circadian function (our body clocks), synchronization, and harmonization on HLBS health through the lifespan, and how can these be used to understand variability in resilience at the cell, organ, and individual levels? |
| **1.B.9** | CC: There is a need to facilitate the development of publically available large data collections to facilitate the study of the natural history and phenotyping of aging patients with congenital heart defects. |
| **Theme C. Demographic Differences in HLBS Health and Disease Risk** | |
| **Theme C Rationale:** *Decisions regarding public health programs, education, and resources need to be based on an understanding of the mechanisms underlying differences in demographic risks, including sex- and race/ethnic-specific differences in the context of changing demographics.* | |
| **1.C.1** | CQ: What are the local and systemic bases for sex-related differences in HLBS health and disease? |
| **1.C2** | CC: There is a need to invest in the development of novel strategies and tools to study and report on effect of sex differences in HLBS systems. |
| **1.C.3** | CQ: What is the level of cardiometabolic risk (a group of risk factors for atherosclerotic vascular disease and diabetes) in subpopulations compared to aggregate data (e.g., some Asian Americans subpopulations are at higher risk for cardiometabolic disorders when compared to aggregate data)? |
| **1.C4** | CQ: How can cardiometabolic risk be managed to improve health trajectories in different demographic populations? |
| **1.C.5** | CC: There is a need for the development of predictive modeling and prevention trials in populations at high risk for highly prevalent HLBS diseases. |
| **Theme D. Systems Biology** | |
| **Theme D Rationale:** *The normal HLBS systems' function involves complex interactions within and between different biological domains that are often difficult to capture but important to our understanding of the underlying regulatory mechanisms. Also, multi-scale integration of molecular, cellular, and tissue events and interactions and the impact on whole system architecture and function is needed to understand normal biology and the role that disruptions of those normal processes play in disease risk. Systems biology approaches offer the opportunity to integrate contextual, multidimensional, and diverse biological information and can help provide a more complete understanding of the mechanisms that contribute to the expressed phenotype.* | |
| **1.D.1** | CQ: What are the main mechanisms that allow individual HLBS cells and tissues to sense, integrate, and respond to individual and combined mechanical cues and influences at the local and systemic levels? What are the key molecular, structural, and functional participants in mechano-sensing in various HLBS contexts? |
| **1.D.2** | CQ: What are the basic mechanisms that direct interaction of blood cells with each other and the internal or external environment? How do these interactions direct or influence function? How do contact materials affect function of blood cells and what is the optimal handling of such cells? What signals do cells receive by contact with foreign surfaces that influences their future function? |

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| **1.D.3** | CC: There is a need for the development and application of comprehensive single cell biology analytics. Recent advances in the fields of imaging, gene editing (e.g., CRISPR/Cas9), whole-genome RNA and protein analysis, and understanding protein complexes and the higher structural organization of DNA allow for measurements at the single cell level that were not possible previously. Remaining challenges include the design and implementation of multi-scale and cross-disciplinary strategies that incorporate these advances to facilitate an integrated understanding of the mechano-sensing processes, cellular interactions and implications in HLBS health and disease risk. |
| **1.D.4** | CQ: What -omic signatures define the normal vasculome (gene expression patterns in the vascular endothelium) of the different vascular beds that surround HLBS tissues/organs? |
| **1.D.5** | CC: There is a need to delineate the pathways and mechanisms by which gene expression is modified (i.e., the epigenetic changes) as well as identify and determine the role of the contributing proteins in normal hematologic systems. |
| **1.D.6** | CC: There is a need to leverage the dramatic progress in proteomics to establish cause and effect mechanisms of HLBS systems. |
| **1.D.7** | CQ: What is the level of functional complexity of gene regulatory network variation from a single cell to an entire population? |
| **1.D.8** | CQ: How do various gene regulatory networks communicate and influence each other across HLBS systems? |
| **1.D.9** | CC: There is a need to develop investigational models, from single cells to organs systems to experimental animals, to identify key factors in gene networks. |
| **1.D.10** | CC: There is a need to stimulate basic research to gain fundamental knowledge of post-translational modifications, including the glycome (the entire complement of sugars in our body), its regulation, and function in HLBS systems; train researchers to gain working knowledge of glycobiology; and establish local infrastructure to facilitate collaboration and provide expertise on a larger scale. |
| **1.D.11** | CC: There is a need to delineate the role of non-coding RNA in HLBS systems, especially lncRNAs, to help design novel therapeutic approaches. |
| **1.D.12** | CQ: What are the roles of RNAs (e.g., microRNAs, lncRNAs, etc.) in HLBS systems' growth, adaptation, and injury healing response? |
| **Theme E. Developmental Biology** | |
| **Theme E Rationale:** *A greater understanding of normal and disordered development of HLBS systems is necessary to advance our understanding of normal development, altered development, normal variation, and normal injury and repair mechanisms. This knowledge can be used to optimize health across the lifespan. Additionally, knowledge of basic biology in these areas can be leveraged to combine with advances in material sciences to develop self-adjusting bioengineered devices that will support, correct, and/or replace cellular, tissue, or organ functions to maintain normal function and advance regenerative medicine.* | |
| **1.E.1** | CC: There is a need to catalyze the development of standardized cell culture protocols to establish and maintain cell lines relevant to functional studies of HLBS systems. This resource would facilitate the availability of hard-to-culture cell lines, expand the number of HLBS cell lines and improve reproducibility across studies. |
| **1.E.2** | CQ: How can endogenous repair mechanisms and alterations of stem cell (e.g., stem cell) cycles be harnessed to promote regeneration of the lung? How do lung stem cells recognize appropriate niches, and what cell-cell interactions mediate normal repair? What |

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| | characteristics define lung stem cell niches? What controls proliferation and differentiation of lung stem cells in normal repair? |
| **1.E.3** | CC: New tools and knowledge are required to leverage our understanding of the surrounding milieu, including structural and matrix biology, and lung development to better understand injury, regeneration, and repair of the normal (or developing) lung as a basis for regenerative medicine. |
| **1.E.4** | CC: There is a need to leverage ongoing research on active materials (e.g., self-regenerating body armor, insulin-releasing polymers that respond to glucose, etc.) to stimulate the invention of new materials and constructs that are electrically, chemically, and mechanically active to enable self-adjusting bioengineered implants. |
| **1.E.5** | CC: There is a need to understand the specific contribution of epigenetic, genetic, and environmental influences on developing HLBS systems. |
| **Theme F. Determinants of Health and Disease Risk** | |
| **Theme F Rationale:** *Many chronic diseases are thought to have origins in early life due to complex interactions between an individual's genetic risk and environmental exposures. There is a need to define the events and mechanisms that confer risk or protection for the development of chronic diseases/disorders so that the natural history of protective and risk states is better defined and can be used to develop primary prevention strategies. Additionally, variation, resilience, and extreme responses to environmental exposures across the lifespan need to be understood, such that biomarkers and interventions based on understanding biologic response can be developed and utilized to potentiate HLBS health across the lifespan. This includes long-term treatment outcomes for early life diseases/disorders.* | |
| **1.F.1** | CQ: What is the relationship between physiological and pathophysiological development of blood vessels (angiogenesis) and placental function in at-risk pregnancies? |
| **1.F.2** | CQ: What are the inflection points at which the body's normal physiologic equilibrium (homeostasis) becomes dysregulated that may lead to the development of chronic diseases? |
| **1.F.3** | CQ: What are the molecular and cellular responses in the lung that occur after environmental stimuli that predict homeostatic resilience or transition to disorder or aging? |
| **1.F.4** | CC: There is a need to facilitate multi-scale methodologies that combine objective measures and biomarkers of dietary intake to identify deficiencies/excesses that contribute to risk for cardiometabolic diseases and informs effective intervention strategies. |
| **1.F.5** | CC: There is a need to support and facilitate efforts to understand the specific contribution of epigenetic, genetic, and environmental influences on developing organ systems. |
| **1.F.6** | CQ: How can we better understand molecular and physiological mechanisms of hypothermia to delineate the difference between beneficial hypothermia and uncontrolled shock-induced hypothermia? |
| **1.F.7** | CQ: What is the measureable normal human variation at the -omic, cellular, organ, and system levels within the population and across the lifespan? |
| **1.F.8** | CQ: What are the mechanisms of resilience at the molecular, cellular, organ, and system levels that act to maintain health? Do these differ over time and by sex? |
| **1.F.9** | CQ: What factors render individuals or populations, subject to the same exposures, as resilient or susceptible to disease? Do these differ over time and by sex? |
| **1.F.10** | CQ: What are the molecular and cellular variations in regional areas of the lung and what |

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| | controls these variations? |
| **1.F.11** | CQ: What are the mechanisms that underlie extreme adaptation in HLBS systems in extreme conditions? How can this knowledge be used to develop novel interventions that optimize health or may be used for primary prevention? |
| **1.F.12** | CQ: What are the major determinants of individual differences in sleep behavior? |
| **1.F.13** | CC: There is a need for tools and algorithms for robust and objective evaluations of sleep health biomarkers. |
| **1.F.14** | CC: What are the molecular and behavioral mechanisms involved in maintaining healthy weight across the lifespan? |

## Goal 2: Reduce Human Disease

| ID No. | CQ/CC |
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| **Theme A. High-Gain Opportunities for Studies of Pathobiology** | |
| **Theme A Rationale:** *Serious clinical problems associated with HLBS diseases may be solvable if researchers can better understand the underlying pathobiology of these conditions. That kind of fundamental research becomes an especially high priority when (1) the disease process leads to severe illness and when (2) new technologies or experimental approaches provide an opportunity to resolve important issues in the field. The following questions identify areas in which mechanistic research may soon provide a leap forward in understanding, leading to much more effective interventions for prevention or treatment of HLBS diseases*. | |
| **2.A.1** | CQ: What is the pathophysiology of heart failure with preserved ejection fraction (HFpEF), and how can this condition be better diagnosed and treated? |
| **2.A.2** | CQ: What is the pathobiology of fibrosis that accounts for its organ specificity (often affecting lung, heart, or bone marrow alone), its progression in the absence of apparent stimuli, and its resistance to drug therapy? |
| **2.A.3** | CQ: What are the mechanisms for the late development of complications or new clinical problems after hematopoietic cell transplantation (HCT)? How can these consequences be detected early and prevented to reduce the high rates of mortality following HCT? |
| **2.A.4** | CQ: What pathobiology underlies non-obstructive ischemic heart disease and the associated risks for acute coronary syndrome and early mortality? What features (e.g., biochemical, vascular, autonomic, environmental, or psychosocial) identify mechanistically distinct patient groups that could be targeted for treatment and secondary prevention? |
| **2.A.5** | CQ: What biomarkers of acute environmental exposure are predictive of disease onset or progression? What biological effects represent irreversible responses? |
| **2.A.6** | CQ: What are the pathobiological mechanisms that govern the conversion of chronic HLBS conditions into acute disease (e.g., sickle cell disease (SCD) to crisis, coronary artery disease (CAD) to myocardial infarction (MI), chronic obstructive pulmonary disease (COPD) to exacerbation)? How can we identify biomarkers to predict and therapies to prevent these transitions? |
| **2.A.7** | CQ: What pathobiology underlies vascular causes of cognitive decline? What early interventions would target this pathobiology to maintain cognitive function? |
| **2.A.8** | CQ: What are the mechanisms whereby congestive heart failure causes lung remodeling and leads, in end-stage disease, to right ventricular failure? |
| **2.A.9** | CQ: What is the pathobiology of aberrant calcification of coronary arteries and heart valves, and why is calcification associated with worse prognosis? |
| **2.A.10** | CQ: What interdependencies between the brain/peripheral nervous system and the heart/vascular systems are important to the development, progression, manifestations, and treatment of cardiovascular (CV) disease? |
| **2.A.11** | CQ: What mechanisms underlie the susceptibility of some individuals, especially women, to insomnia? |
| **2.A.12** | CQ: What are the mechanisms whereby psychosocial stress contributes to the onset, progression, and morbidity of ischemic heart disease? |

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| **Theme B. Redefining Concepts of Disease and Health** | |
| **Theme B Rationale:** *Multisystem and multidisciplinary investigations of disease models that integrate individual patient and population data may help to refine definitions of disease and health and identify subgroups of patients by their molecular pathophysiology, rather than by traditional classification schemes. Such subcategorization of diseases may allow more optimal matching of interventions with the appropriate patients – fulfilling the promise of precision medicine. Enhanced descriptions of disease may also help to identify novel targets for intervention.* | |
| **2.B.1** | CQ: What underlies secondary resilience, such that some people are protected from the complications of HLBS diseases? |
| **2.B.2** | CC: Clinical evaluation tools are needed to differentiate patients with atherosclerotic heart disease who will progress to MI or sudden cardiac death from those with stable atherosclerotic heart disease. |
| **2.B.3** | CQ: What are biomarkers of pulmonary hypertension that could inform pathobiology and guide treatment? |
| **2.B.4** | CQ: What genetic, biomarker, and environmental predictors of risk and outcome would inform and improve management of SCD and secondary prevention of its progression and complications? |
| **2.B.5** | CQ: Which phenotypic, biomarker, and molecular characteristics, when applied in clinical trials, predict differential responses to therapy in individuals with chronic HLBS diseases? |
| **2.B.6** | CQ: What tests would identify individuals who are at high risk of venous thromboembolic events and would benefit from targeted risk factor modification and/or intensive prophylaxis? |
| **2.B.7** | CC: Clinical evaluation tools are needed for assessing operative risk and predicting postoperative recovery in the elderly. Possibilities include biomarkers of physiologic age and a clinical score for frailty. |
| **Theme C. Working Toward Primary Prevention, Disease Reversal, and Cure** | |
| **Theme C Rationale:** *Leveraging novel technologies and recent knowledge gains has placed the tantalizing potential for cure of some HLBS diseases within reach. Further research is needed to develop innovative therapeutic approaches, to align these with the most amenable diseases and patient subgroups, and to rigorously test their safety and efficacy.* | |
| **2.C.1** | CQ: How can improved methods for hematopoietic cell transplantation or gene therapeutic approaches be used to cure SCD? |
| **2.C.2** | CQ: How can interventions in pregnancy or early childhood designed to modulate immune development (e.g., antiviral prophylaxis) result in primary prevention of asthma? |
| **2.C.3** | CQ: What management strategies are efficacious for preventing or reversing myocardial fibrosis? |
| **2.C.4** | CQ: How do lung stem/progenitor cells and defects in these cells contribute to the onset and progression of chronic pulmonary diseases? |
| **Theme D. Critical Issues in Clinical Management** | |
| **Theme D Rationale:** *Evidence-based practice can substantially improve health outcomes, but this requires systematic testing of interventions and management strategies through appropriately designed investigations. Critical gaps remain in knowledge of how to manage certain HLBS clinical situations, and well-designed studies are needed to fill these gaps.* | |

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| **2.D.1** | CQ: What is the optimal clinical management approach for patients with severe calcific aortic stenosis but minimal symptoms? |
| **2.D.2** | CQ: What are the optimal red blood cell transfusion thresholds in both pediatric and adult patients, especially in the context of anemia due to chemotherapy? |
| **2.D.3** | CQ: Do interventions to improve ventilation during sleep improve morbidity and mortality in individuals with both heart failure (or other diseases associated with chronic hypoxemia) and sleep disordered breathing? |
| **2.D.4** | CQ: What effective and implementable practices would reduce the rate of mortality associated with out-of-hospital cardiac arrest? |
| **2.D.5** | CQ: What *ex vivo* processing of blood products (e.g., washing, rejuvenation, or leukocyte reduction) would reduce the toxicity and morbidity of blood transfusions? |
| **2.D.6** | CQ: What is the best strategy for preventing and treating CV problems in patients with COPD who are at enhanced risk of CV events and whose clinical care is often complicated by comorbidity and polypharmacy? |
| **2.D.7** | CC: Better tools are needed for evaluating aortic aneurysms and deciding when to attempt a repair, including animal models that reflect human pathology and biomarkers/molecular imaging tools that are predictive of rupture or dissection. |
| **2.D.8** | CQ: In the context of anticoagulation in atrial fibrillation, would warfarin therapy with INR self-testing and online "virtual clinic" monitoring and management yield lower rates of thromboembolism and major bleeding than are achieved with the newer oral anticoagulants? |
| **2.D.9** | CQ: Which patients benefit from rehabilitation treatments (cardiac and pulmonary) and how can the benefits of rehabilitation treatments be sustained long term? |
| **2.D.10** | CQ: What is the best strategy for reducing CV morbidity and mortality in cancer survivors (especially breast cancer) who are at enhanced risk of CV events and whose clinical care may be complicated by both comorbidity and drug toxicity? |
| **2.D.11** | CQ: What technical improvements in the processing and storage of red blood cells would improve their potency, safety, and lifetime? What biomarkers or other characteristics predict stability during storage and transfusion success? |
| **2.D.12** | CC: There is a need for sex/gender-specificity in guidelines for clinical management of CV conditions (including treatment following MI, non-obstructive ischemic disease, and risk for MI associated with diabetes) that is strongly based on understanding of the underlying biology and on clinical evidence. |
| **Theme E. Transformative Opportunities for Data Collection and Analysis** | |
| **Theme E Rationale:** *Health information on individuals and populations is expanding at a dramatic pace. Integrating that data – from the genome to environmental exposures – at the individual level can provide a much richer picture of health and disease. Integrated analyses of "big data" may lead to insights into pathobiology and suggest better approaches for disease management and public health.* | |
| **2.E.1** | CC: There is a need for integrated analysis of expanding collections of health information from individual patients – which may soon include genetic, epigenetic, and -omic data – to allow more precise medical management, especially among minority groups that are understudied (e.g., Asian Americans) or have disparate morbidity and mortality (e.g., African Americans). |
| **2.E.2** | CC: There is a need for coordinated access to data from deeply phenotyped NHLBI cohorts and biomarker/imaging/omics studies, including the creation of a scientific commons, to |

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| | promote discovery of key drugable targets and development of novel, efficacious, and individually precise treatments for HLBS diseases. |
| **2.E.3** | CC: Novel analytical approaches are needed to exploit the wealth of knowledge coming from studies of electronic health records, genetics, epigenetics, transcriptomics, metabolomics, proteomics, and systems biology to define disease sub-types, predict risks, and identify therapeutic targets. |
| **2.E.4** | CC: There is a need to facilitate integration of currently siloed registry data and research data sets to cost-effectively expand research on the molecular genomics and pathobiology of congenital heart disease. |
| **2.E.5** | CC: Integration of multidimensional and multidisciplinary data is needed to develop predictive and actionable models of the role of obesity in the risk, prevention, and treatment of cardiopulmonary and sleep disorders. |
| **Theme F. Innovative Approaches and Strategies** | |
| **Theme F Rationale:** *Many unsolved challenges in HLBS conditions remain. Moving the field forward will require advances in technology, novel therapeutic strategies, and creative, out-of-the-box thinking.* | |
| **2.F.1** | CQ: Is targeted manipulation of epigenetic modifications (distinct from global suppression of histone acetylation or DNA methylation) a useful strategy for therapeutic intervention in chronic cardiopulmonary or blood diseases? |
| **2.F.2** | CQ: Would circadian-based strategies (e.g., timing of medication) improve the efficacy of treatments for HLBS diseases (e.g., hypertension, nocturnal asthma, thrombosis, or obesity/diabetes)? |
| **2.F.3** | CQ: How should the management of diseases that typically develop in childhood (including childhood interstitial lung disease, SCD, congenital heart disease, cystic fibrosis, and asthma) be modified as affected individuals mature into adulthood? |
| **2.F.4** | CQ: Could treatment of SCD based on apheresis procedures provide the clinical benefits of blood transfusion without the risks and complications that are associated with both simple and exchange transfusions? |
| **2.F.5** | CQ: How can real-time, individual-level monitoring be used to detect and predict electrical instability of the heart and to prevent sudden cardiac death? |
| **2.F.6** | CC: There is need for better animal and multicellular *in vitro* models that reproduce the biochemical abnormalities of HLBS diseases, reflect the importance of molecular targets in those diseases, and predict the efficacy of particular drugs in their treatment. |
| **2.F.7** | CQ: Would a systems biological approach to understanding the immune system support the design of more efficacious treatment strategies for chronic inflammatory and autoimmune HLBS diseases? |
| **2.F.8** | CC: A variety of “smart” devices are needed that both monitor physiology and assist, adjust, or intervene automatically to treat acute complications of CV disease in an optimal way. |
| **2.F.9** | CC: Multidisciplinary, multinational partnerships are needed to develop effective and sustainable strategies for combating chronic HLBS disorders in developing nations – addressing the highly variable local epidemiology of HLBS disorders, the need for novel approaches to reducing disease burden, and the challenges of implementation in developing countries. |
| **2.F.10** | CQ: Are imaging measures clinically useful biomarkers of metabolic syndrome and |

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| | cardiopulmonary disease? |

## Goal 3: Advance Translation Research

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| **Theme A. Advancing Early Stage Translational Research in HLBS Disorders** | |
| **Theme A Rationale:** *There are specific bottlenecks in the translational path that impede movement from basic discovery to the identification of new diagnostics and therapeutics. The first of these is situated between discovery science and proof-of-concept in preclinical models. The next lies between preclinical studies and early phase human research. Facilitation of progress around these obstacles should serve to greatly increase future diagnostic and therapeutic options.* | |
| **3.A.1** | CC: There is a need to attract private-sector funding and multiple partnerships earlier in the product development process to help bridge the gap between academic discoveries and product commercialization. |
| **3.A.2** | CC: There is a need to support translational skills development and training, including the navigation of pre-IND (investigational new drug) phases of translational science. |
| **3.A.3** | CQ: What approaches can be pursued to centralize and expand existing resources to enable accessibility by interested translational investigators? |
| **3.A.4** | CQ: How can new discoveries about molecular, cellular, and tissue-based arrhythmia mechanisms be more rapidly translated into better therapeutic and preventive strategies? |
| **Theme B. Addressing Gaps in HLBS Implementation Research** | |
| **Theme B Rationale:** *Providers recommend, and patients receive, only a small proportion of proven preventive and therapeutic interventions. It is currently unclear which implementation approaches will most effectively improve upon this low level of adoption. Identifying those interventions with the greatest impact will serve to decrease mortality and improve quality of life.* | |
| **3.B.1** | CQ: What are the best ways to enhance methodologic approaches to implementation research? New methodologies are needed to approach questions such as: How to apply broad scientific evidence to specific sub-populations and how to predict and evaluate the impact of an evidence-based test or intervention? |
| **3.B.2** | CQ: What are effective implementation strategies to translate robust evidence into clinical practice and to ensure multilevel input from patients, providers, and health systems? |
| **3.B.3** | CQ: What are the best implementation strategies to improve adherence to evidence-based practices, prescribed medications, and behavioral and medical regimens? |
| **Theme C. Optimizing Data Integration and Analysis** | |
| **Theme C Rationale:** *Advances in science and technology have produced a wide range of data types and platforms. Only a small proportion of this vast array of information is currently being well-integrated and optimally analyzed. Maximizing data operations will offer extraordinary opportunities to advance medical science and improve population health.* | |
| **3.C.1** | CC: There is a need to better utilize existing data and repository samples that have been derived from large cohort studies. By fostering broad data integration and well-planned sample analyses, previous investments in these large cohorts can be maximized. |
| **3.C.2** | CC: There is a need to apply bioinformatics approaches to the analysis of electronic health records (EHRs) and other types of “big data.” Such approaches could inform our understanding of best practices, foster clinical research, expedite bedside-to-basic (reverse) translational research, as well as inform observational and implementation research in HLBS |

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| **3.C.3** | CC: There is a need to ensure better use and integration of “omics” data types (genetics, epigenetics, transcriptomics, metabolomics, proteomics, etc.) to identify markers of HLBS disease sub-types, risk, and prognosis. |
| **3.C.4** | CC: There is currently insufficient infrastructure to accommodate HLBS-related genomic sequencing data. The development of appropriate infrastructure would enable more consistent sharing, interpretation, and clinical application of these important datasets. |
| **3.C.5** | CC: There is a need for ontology-backed deep phenotyping of subjects/patients who are represented in established cohorts and databases. This will allow informative relationships to be established between disease phenotypes and genotypes, and thereby accelerate translational research. |
| **3.C.6** | CC: There is a specific need to develop sleep and circadian disorder registries in order to appropriately study these entities. Current clinical research in sleep and circadian disorders depends on cohorts designed for other purposes. There are limitations to using these cohorts, including the lack of appropriate in-depth phenotyping data and the inadequate reliability of diagnostic criteria. |
| **3.C.7** | CQ: How can one harness data associated with health system quality improvement (QI) activities so as to better facilitate research and implementation endeavors? Challenges include the need to harmonize data coming from diverse systems and the need to address human subject research regulations. |
| **Theme D. Reforming Clinical Trials** | |
| **Theme D Rationale:** *Traditional clinical trials are extremely expensive and labor intensive. Multiple complexities compromise the efficiency of these trials and standard designs are frequently not suitable for evaluating many types of HLBS sub-populations and disorders. Innovative new trial paradigms and resources will greatly accelerate clinical research and associated health discoveries.* | |
| **3.D.1** | CC: Creative approaches to clinical trials in rare HLBS diseases are needed to successfully test strategies that will broaden preventive and therapeutic options. |
| **3.D.2** | CQ: What approaches can one use to overcome barriers to timely trial completion? Delays currently retard advancement of preventive practices and therapeutic options. |
| **3.D.3** | CQ: What methods can be employed to successfully use EHR clinical and laboratory data to randomize subjects to appropriate treatment options? How can broad consent be obtained? |
| **3.D.4** | CQ: How can one leverage existing registries to perform prospective trials at reduced cost? |
| **3.D.5** | CQ: How can key stakeholders, including Federal agencies and private entities, be brought to the table to engage in a broad discussion to transform the clinical trial infrastructure? |
| **3.D.6** | CC: There is a need to encourage creative uses of new data sources, such as social media, in clinical trials and foster approaches that will improve clinical trial efficiency, cost effectiveness, and generalizability. |
| **3.D.7** | CQ: What clinical trial approaches can be used effectively to study the chronobiology of drug delivery? |
| **Theme E. Promoting Team Science** | |
| **Theme E Rationale:** *Scientific discovery increasingly requires a wide range of specialized capabilities, many of which have not traditionally been collectively utilized in medical research. Enhancing the depth* | |

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| *and breadth of expertise will bolster innovative problem-solving and accelerate translational endeavors.* | |
| **3.E.1** | CC: Given current scientific complexities, a strategy should be defined that can more aggressively promote synergies among various groups. Examples of these groups include MDs and PhDs; investigators focused on basic research and scientists conducting patient-oriented research; engineers and clinicians; subspecialists, generalists, and bioinformatics experts; representatives from academia, non-profits, and industries; etc. Such collaborations will enhance and expedite advances in HLBS disorders. |
| **3.E.2** | CC: There is a need to encourage the formation of multi-disciplinary data analysis teams that can provide in-depth and strategic analysis of existing genomic data sets to yield findings that will enhance translational research. |
| **Theme F. Transforming Technologies to Address HLBS Disorders** | |
| **Theme F Rationale:** *There have been an ever-increasing number of technologic and engineering breakthroughs over the past two decades. Many of these have occurred in the context of medical research, but a substantial number have emerged from work in other fields. In the coming years, new technologies must be explored and existing capabilities further refined so that basic discoveries can be successfully translated into new diagnostic/therapeutic devices, better data acquisition and analyses, and improved health surveillance and educational modalities.* | |
| **3.F.1** | CC: There are a number of challenges related to the development of the next generation of ventricular assist devices (VADs). These challenges include minimizing platelet activation, thrombogenesis, and bleeding; developing better percutaneous and transcutaneous systems; and improving battery and charging-mechanism designs. |
| **3.F.2** | CC: Current apheresis techniques are non-specific and have changed little in recent decades. Newer, safer, and more efficient approaches are needed to meet the unique requirements of patients with specific blood disorders. |
| **3.F.3** | CQ: How can one promote new breakthrough technologies that will address the current gaps in cardiovascular engineering? |
| **3.F.4** | CQ: How can emerging computed tomography (CT) techniques (such as spectral, phase contrast, and nanoparticle contrast) and other imaging techniques be effectively integrated into patient care? |
| **3.F.5** | CC: There is a need to develop hand-held portable technologies that can assist paramedics in collecting and transmitting data during out-of-hospital cardiovascular emergencies. |
| **3.F.6** | CQ: How might social media platforms, such as Facebook and Meetup, be leveraged to design low-cost research studies and interventions that promote sustainable healthy lifestyles and behaviors? |
| **Theme G. Enhancing Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) Opportunities in Non-Malignant Disorders** | |
| **Theme G Rationale:** *Substantial progress has been made treating malignant blood disorders with allogeneic HSCT. Complications such as graft versus host disease (GVHD) and transplant rejection have been mitigated and alternative donors have been successfully utilized. The field is now well-poised to explore further research and refinements that would permit the use of this potent modality to treat and cure non-malignant disorders.* | |
| **3.G.1** | CQ: How can we optimize HSCT safety and make the procedure a more universally effective treatment for non-malignant blood and immune disorders? |
| **3.G.2** | CQ: How can we use novel agents to provide more selective immunosuppression for patients |

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| | who receive allogeneic HSCT? Such therapies would target donor immune responses that are related to graft-versus-host disease while preserving pathogen-specific host immunity so that HSCT can be applied to a broader range of non-malignant diseases and to recipients who lack well-matched donors. |
| **Theme H. Finding Alternatives to Current Transfusion Practices** | |
| **Theme H Rationale:** *Scientific breakthroughs and innovative bioinformatics have made more proactive approaches to blood safety and availability possible. In addition, recent laboratory discoveries and emerging manufacturing technologies have made the concept of artificial blood products a foreseeable reality.* | |
| **3.H.1** | CC: There is a need to develop the necessary research infrastructure and expertise to address new and emerging threats to the safety and availability of the US blood supply. |
| **3.H.2** | CC: There is a need to develop safe, well-functioning designer platelets and red blood cells, as well as the large-scale production of these products for therapeutic and diagnostic use. |
| **3.H.3** | CC: There is a need to advance research regarding the physiologic processes that govern safe and effective oxygen delivery outside the red blood cell. |
| **Theme I. Promoting Life-Span Research Approaches** | |
| **Theme I Rationale:** *Current "risk-factor" research most often addresses populations already affected by disease. Early contributing behaviors, environmental issues, and genetic/epi-genetic underpinnings of disease evolution are poorly appreciated, as disease risks are generally not evaluated in a prospective fashion. A life-span perspective will allow investigators to identify important interdependent risk factors that pre-date disease. This knowledge base can then be translated into more effective preventive and therapeutic strategies.* | |
| **3.I.1** | CQ: Will reduction of known risk factors during childhood and adolescence translate into the prevention or delayed development of atherosclerosis and other heart diseases? |
| **3.I.2** | CC: There is a need to integrate existing electronic pediatric clinical data into a comprehensive data repository. By so doing, HLBS disease risk factors and outcomes can be better delineated. Such an approach will inform translational research and resulting preventive strategies. |

# Goal 4: Develop Workforce and Resources

| ID No. | CQ/CC |
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| **Theme A. Career Continuum** | |
| **Theme A Rationale:** *One of the NHLBI's enduring aims is to train and nurture a diverse biomedical workforce. Achieving this goal requires that*<br>• *Students from diverse backgrounds, at each stage of education (e.g., kindergarten through college), are exposed to the wonders of science;*<br>• *During the stages of higher education and scientific training (e.g., medical/graduate school, postdoctoral, residency, and fellowship training) and through the early and mid-career stages, trainees have strong incentives to pursue and maintain scientific careers; and*<br>• *Senior scientists give back by mentoring the next generation.*<br>*Ensuring a diverse talent pool at each of these stages and through the transitions between stages will help promote and sustain a research workforce that has diverse perspectives, experiences, and research interests and that therefore is more likely to investigate the many varied aspects of HLBS biology.* | |
| **4.A.1** | CC: Training programs are currently designed to support individual career stages (e.g., the graduate/medical education stage, the postdoctoral/fellowship period, and the junior investigator stage). However, there is a need for better support during the transition between these stages, when scientists are lost from the pipeline. |
| **4.A.2** | CQ: What kinds of exposures, beginning in elementary school, would stimulate students' interest in science, particularly those from diverse and disadvantaged backgrounds? |
| **4.A.3** | CQ: What changes can be made in scientific training and research support so that research careers have greater appeal and can more effectively compete with other options, such as careers in business and health care? There are many disincentives to pursuing research careers (e.g., long training duration, low entry-level income, and career instability). Moreover, students from disadvantaged backgrounds may be especially wary of careers that present continued financial struggle and uncertainty. |
| **4.A.4** | CQ: How can we ensure that there are sufficient numbers of clinician scientists, particularly those interested in pursuing the translational breakthroughs from basic science laboratories? How do we identify and encourage medical students who have not yet chosen research career paths to do so (i.e., what kinds of incentives can be provided)? |
| **4.A.5** | CQ: How can research training programs that include research on diseases or conditions that disproportionately affect minority populations (e.g., obesity) attract minority researchers and help sustain their careers? |
| **4.A.6** | CQ: How do we attract more students/trainees into traditional research fields (e.g., physiology, integrative biology) that are as critical to advancing science as emerging fields (e.g., "omics" and big data) but do not have the same cache and are thus on the decline? |
| **4.A.7** | CC: We lack coherent mechanisms, particularly cross-training of MDs and PhDs, for training the next generation of translational researchers, and this shortcoming may impair needed interactions between clinicians and basic researchers. |
| **4.A.8** | CQ: The period between the end of the K award and the first R01 is a critical transition wherein many trainees opt out of a science career and pursue other viable sources of income, such as work in the clinic, in teaching, or in the private sector. What can the research community (e.g., research institutions, NIH, etc.) do to entice and support young investigators (potential and actual K award applicants) to transition to R award funding and become independent scientists? |

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| **4.A.9** | CC: Although there are programs to increase the funding of early career investigators, and many senior scientists obtain continuing renewal, there are no programs dedicated to helping scientists maintain funding in the middle stages of their career. |
| **4.A.10** | CQ: How can senior scientists be encouraged to focus more on mentoring young investigators and, in the later stages of their career, to entrust greater responsibility to emerging lab leaders (e.g., incrementally turning over their projects to more junior lab members)? |
| **4.A.11** | CC: There is a need to ensure that accomplished scientists have adequate skills, time, and incentives to mentor successfully. |
| **Theme B. Professional Development** | |
| **Theme B Rationale:** *Throughout the career continuum, scientists need to be better trained in the business aspects of research and in applying business processes to improve research efficiency and value. We currently train scientists in specific disciplines, but we do not train them in how to run a lab, manage a budget, etc. Moreover, there are skill sets that cut across disciplines, such as understanding commercialization, bioinformatics, communications, reproducibility, implementation science, and health inequities, that are critical to enhancing any scientific career path and can open the doors to a broader array of scientific career options.* | |
| **4.B.1** | CQ: How do we ensure that trainees across the career continuum are aware of — and, if interested, prepared for — a variety of possible scientific career opportunities (e.g., careers in teaching, industry, or government)? |
| **4.B.2** | CQ: How do we best develop a scientific workforce that is fluent in product development and commercialization issues, including regulatory, intellectual property, and business issues? There is a need for scientifically trained experts from diverse backgrounds who understand business needs relevant to biomedical technology development and possess both the depth and breadth of knowledge needed to bring products for HLBS indications to the market. |
| **4.B.3** | CQ: Should training in biostatistics, computer science, and bioinformatics become broader for the entire biomedical community in this era of very large data sets? |
| **4.B.4** | CQ: What are the best strategies to develop a highly competent and diverse implementation science research workforce (i.e., researchers, reviewers, and investigators) to address health inequities (domestic and abroad)? |
| **4.B.5** | CC: There is a need for increased training of biomedical and behavioral researchers in rigorous scientific practices so that these researchers can produce results that have greater reliability and reproducibility. |
| **4.B.6** | CQ: How do we add communication skills to our training programs to improve scientists' communication with the public? How do we also improve the ability of basic and clinical scientists to understand each other's scientific language and appreciate the importance of the other's research questions and findings? |
| **Theme C. Analytics, Metrics, and Outcomes** | |
| **Theme C Rationale:** *We need to understand the current state of the workforce, determine ways to identify individuals' and programs' potential for success, and develop metrics of success for individuals and programs. Understanding these issues will inform and improve the implementation and design of training strategies.* | |
| **4.C.1** | CC: A concerted effort is needed across different Institutes and other organizations involved in training researchers, such as the Robert Wood Johnson Foundation, to collect and combine common data related to the biomedical research workforce (i.e., credible human resource and |

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| | labor market data); data collected should include information on the educational achievements and employment status of scientists over time, metrics of success at different career stages (e.g., publications, subsequent grants, or training), and training program characteristics (e.g., length and intensity of training, training content, mentoring components, research components, etc.). |
| **Theme D. Collaborations and Partnerships** | |
| **Theme D Rationale:** *To maximize the productivity of the scientific enterprise, we need to capitalize on new opportunities for collaborating not only across disciplines but also across institutions (e.g., minority-serving and research-intensive institutions) and sectors (e.g., the public and private sectors).* | |
| **4.D.1** | CQ: Would the creation of "Centers of Excellence" akin to NCI's Comprehensive Cancer Centers encourage partnerships with local institutions, thereby facilitating more research with less federal support? |
| **4.D.2** | CQ: Would requiring collaborations across multiple institutions promote advances in research due to complementary expertise, sharing of resources, combining scientific efforts, etc.? |
| **4.D.3** | CC: There is a need for the NHLBI to engage in public-private partnerships to increase the pool of available funding opportunities. |
| **4.D.4** | CC: There is a need for competitive research training strategies that embrace the role of multi-institutional and professional scientific organization research collaboration. |
| **4.D.5** | CC: There is a need for collaboration with the health care community to improve education of health care workers in evidence-based care. When these workers lack basic knowledge of the key components of evidence-based care, it can result in poor health outcomes for those they care for, especially patients with sickle cell disease. Evidenced-based curriculum should be available for all health care providers. |
| **4.D.6** | CC: To enhance diversity in the biomedical workforce, institutions that are less research intensive, such as some of the historically black colleges and universities, Hispanic-serving institutions, and tribal colleges and universities with primarily minority faculty and/or student bodies, may need additional support for training researchers. |
| **Theme E. New Educational Resources to Enhance Training Efficiency** | |
| **Theme E Rationale:** *One major disincentive to pursuing research careers is the duration of training required, delaying the establishment of fruitful careers. New digital learning technologies stand to enhance training efficiency, thereby shortening the education and training process.* | |
| **4.E.1** | CQ: How can we harness virtual learning technologies to address the needs of the modern and future biomedical workforce? Virtual learning tools (e.g., immersive learning simulations and serious games) offer tremendous possibilities for creating effective learning experiences for biomedical scientists and providing them with opportunities to practice research skills within the context of realistic challenges, which can in turn reduce the duration of training. |
| **Theme F. Team Science** | |
| **Theme F Rationale:** *Advances in technology and big data have revolutionized science and have made it more critical than ever to build research teams to study the most complex problems. Scientific training must keep pace with these developments to ensure that scientists understand how to build the teams necessary to tackle a research problem.* | |
| **4.F.1** | CQ: Are training and career development programs sufficiently promoting interdisciplinary and |

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| | team science? Should we change the way these programs are structured? |
| **4.F.2** | CC: There is a need to provide more funding opportunities for collaborative, team science involving clinician scientists, basic researchers, and data scientists as co-investigators. |
| **4.F.3** | CC: Short-term junior faculty training programs, such as the Summer Institute Training Programs for Junior Faculty, need to expand their focus to include diverse disciplines (e.g., cancer, diabetes) and to increase opportunities for networking to prepare scientists for collaborative research. |
| **4.F.4** | CQ: Would using multi-disciplinary teams (nutritionists, exercise physiologists, social workers, nurses, etc.) be an effective approach to applying lifestyle medicine to patient care? |
| **4.F.5** | CC: There is a need to encourage the development and growth in researchers of integrated and multi-disciplinary biomedical research skills, which researchers will need to utilize emerging technology, infrastructure, and paradigms. |